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Application of percolation threshold to disintegration and dissolution of ibuprofen tablets with different microcrystalline cellulose grades

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ABSTRACT

The study presented was conducted to determine whether a percolation threshold value, previously determined for ibuprofen/microcrystalline cellulose (MCC) blends using percolation theory and compression data (Queiroz et al., 2019), could translate to tablet disintegration and dissolution data. The influence of MCC grade (air stream dried versus spray dried) on tablet disintegration and dissolution was also investigated. Complementary to conventional disintegration and dissolution testing, Raman imaging determined drug distribution within tablets, and in-line particle video microscopy (PVM) and focused-beam reflectance measurement (FBRM) monitored tablet disintegration. Tablets were prepared containing 0–30% w/w ibuprofen. Raman imaging confirmed the percolation threshold by quantifying the number and equivalent circular diameters of ibuprofen domains on tablet surfaces. Across the percolation threshold, a step change in dissolution behaviour occurred, and tablets containing air stream dried MCC showed slower disintegration rates compared to tablets containing spray dried MCC. Dissolution measurements confirmed experimentally a percolation threshold in agreement with that determined using percolation theory and compression data. An increase in drug domains, due to cluster formation, and less efficient tablet disintegration contributed to slower ibuprofen dissolution above the percolation threshold. Slower dissolution was measured for tablets containing air stream dried compared to spray dried MCC.

1. Introduction

Disintegration and dissolution profiles are critical quality attributes assessed to evaluate drug release performance (Dressman and Krämer, 2005; Huang et al., 2011; Nickerson et al., 2018). Disintegration is often the rate determining step for drug release, particularly for poorly water soluble drugs (Caramella et al., 1988). Disintegration is the mechanical fragmentation of the compressed tablet into small granules or agglomerates. Disintegration is initiated by liquid penetration in the porous of the compact. Swelling is one of the most accepted disintegration mechanisms, which is characterized by an enlargement of the particles that builds up pressure to fragment the tablet matrix (Markl and Zeitler, 2017). The bonding mechanism during compression and the bonding surface area have a direct impact on tablet disintegration. Swelling depends on an optimal tablet porosity, such that the liquid can enter the tablet matrix. However, large void spaces can supress the swelling action of disintegrants (Desai et al., 2016).

The application of modelling approaches to enhance product knowledge has been motivated by quality guidelines as an alternative to iterative testing approaches during formulation development (International Council for Harmonisation, 2012, 2008, 2005a, 2005b; Kimura et al., 2013). The percolation threshold model has been used to explain how particle–particle interactions of drug and diluents alters dissolution performance of formulations containing different drug loadings (Bonny and Leuenberger, 1993, 1991). In this context, the percolation threshold is the drug loading in which clusters of the drug span throughout the entire volume of the tablet, i.e. an infinite cluster is formed. When this cluster is formed properties of the blend may undergo significant changes (Leuenberger, 1999).

Previous studies determined the percolation threshold value from

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disintegration and dissolution experimental data (Kimura et al., 2007; Stillhart et al., 2017; Wenzel et al., 2017). These studies experimentally determined critical loadings at which disintegration times undergo a step change. These were then assumed to be the percolation thresholds. However, Kimura et al., 2007 recommended further studies to investigate if the change in disintegration behaviour was linked to the formation of the infinite cluster described by the percolation threshold theory (Kimura et al., 2007). Since these earlier studies, technological advancements have provided novel techniques to study drug distribution in tablets and tablet disintegration behaviour. These techniques can be key to providing data to support the percolation threshold concepts and the findings of previous studies.

Spectral imaging techniques have been used to provide in depth information related to drug distribution in pharmaceutical tablets. These techniques can be used to investigate the cluster formation predicted by the percolation theory. Fourier transform infrared spectroscopy (ATR-FTIR), X-ray diffraction (XRD), and Raman spectroscopy are the main techniques employed (Chan et al., 2005; Kazarian and Ewing, 2013; Miller and Havrilla, 2005; Zhang et al., 2005). Among those, advancements in Raman instruments has enabled the technique to rapidly map drug distribution in tablets. Raman imaging instruments have been designed to capture rich spectroscopic data which can be translated to provide high-resolution chemical information for tablets (as low as 1 μm per pixel) and require short acquisition times (approx. 15 min for a tablet of 13 mm diameter) (Ali et al., 2013).

Focused Beam Reflectance Method (FBRM) and in-line Particle Video Microscopy (PVM) are innovative techniques that can give real-time in-situ information regarding disintegration and dissolution performance of tablets. FBRM has been used to monitor the rate and the degree of change in the number of particles and particle structures in a process (Barrett et al., 2011; Gregory, 2009; Simon et al., 2019; Zhong et al., 2020). Measurement of the solid particles using FBRM is performed without the need for sampling and performing off-line analysis. The system gives particle count, dimension and shape information in real time by monitoring changes in the system as they occur (Barrett and Glennon, 1999). PVM provides real-time images of the system allowing the user to visually track changes in the solids over time (Barrett and Glennon, 2002). The imaging window measures an area of approximately 800 μm by 1100 μm. PVM also records a Relative Backscatter Index (RBI) trend which can be used to track changes in the shape and size of solid particles as well as changes in the solids concentration (Werner et al., 2017). RBI is comparable to turbidity monitoring. Increased RBI indicates a larger amount of solids (Hartwig and Hass, 2018). As tablet disintegration progresses the number of particles in the slurry increase as larger particles fragment. Therefore, as disintegration proceeds, more particles are captured in the image and the RBI increases.

FBRM and PVM techniques are commonly used in crystallization studies (mass transfer from solution to solid phase) (Barrett et al., 2011; Hartwig and Hass, 2018; Jiang et al., 2014; Liu et al., 2011; Mitchell et al., 2011; Simon et al., 2019; Simone et al., 2015). FBRM has also been utilized in previous studies to investigate tablet disintegration and dissolution (Coutant et al., 2010; Han et al., 2009; Menning, 2016; Metzler et al., 2017). PVM has the potential to monitor tablet disintegration and dissolution because changes in particle size and shape in suspension are key features observed during tablet disintegration and dissolution.

The aim of this study was to investigate if a step change in disintegration and dissolution behaviour was observed for tablets produced with drug loadings below and above a predetermined percolation threshold. The percolation threshold of these systems was determined in an earlier study using the physical principals of blending and compaction (Queiroz et al., 2019). The model system investigated was tablets produced from binary blends of microcrystalline cellulose (MCC) and ibuprofen (IBU) at a range of ibuprofen mass loadings. Tablets were prepared with two different MCC grades; one spray dried and one air stream dried. The percolation threshold values determined were 19.08% w/w and 17.76% w/w IBU for blends with air stream dried MCC and spray dried MCC, respectively (Queiroz et al., 2019). A secondary study aim was to determine if the grade of MCC altered any changes in disintegration and dissolution behaviour observed.

In the context of the previous and the present study, percolation threshold is a geometric phase transition in which the concentration of ibuprofen particles is high enough to form a cluster that spans throughout the entire volume of the tablet. When this ibuprofen particle cluster is formed, it is anticipated that a step change in properties of the blend will occur. For example, a reduction in flow, compaction and dissolution would be anticipated with ibuprofen particle cluster formation, as ibuprofen has poor flowability and compressibility properties compared to MCC (Al-Karawi et al., 2018; Liu et al., 2008), and is considerably more hydrophobic (Kawabata et al., 2011).

In addition to traditional pharmacopeial disintegration and dissolution techniques, process analytical technologies (PAT), FBRM and PVM, were employed to better understand tablet disintegration behaviour, and hence its influence on drug dissolution. Building on the application of Raman imaging to qualitatively identify clusters of ibuprofen particles (Queiroz et al., 2019), the present study demonstrated how Raman spectroscopy can be used to quantitatively determine the size and the number of ibuprofen clusters formed on tablets surfaces and hence confirm the percolation threshold determined from compaction data. The MCC grades studied, have similar specifications; average particle size of 130 μm determined by laser diffraction, and similar bulk density (0.28–0.33 g/mL for the air stream dried and 0.25–0.37 g/mL for the spray dried). Queiroz et al. confirmed similarities in particle size distribution between grades by dry powder, laser diffraction analysis. Particle analysis employing an image analysis technique, identified morphological differences between MCC grades: the air stream dried grade contained a greater number of particles with needle shaped geometry, while the spray dried grade contained a greater number of spherical-shaped particles (Queiroz et al., 2019).

2. Materials

Emcocel®90 M (spray dried) and Vivapur®102 (air stream dried) were supplied by JRS Pharma (Weissenborn, Germany) and ibuprofen by Kemprotec (Cumbria, UK). The two MCC products studied were medium size standard grades with theoretical bulk density of 0.28–0.33 g/mL for the air stream dried and 0.25–0.37 g/mL for the spray dried MCC. A range of particulate and bulk powder properties of the batches of ibuprofen, air stream dried MCC and spray dried MCC used in this study had been previously determined (Table 1) (Queiroz et al., 2019). Other materials used such as buffer components and HPLC mobile phase were all supplied by Sigma Aldrich, Ireland.

3. Methods

3.1. Tablet manufacture and characterization

Binary blends of MCC and IBU were prepared containing a range of IBU concentrations: 2.5, 5, 7.5, 10, 12.5, 15, 20, and 30% w/w. Each blend, total weight 300 g, was prepared using a cube mixer KB 15 (Erweka, Heusenstamm, Germany) at 30 rpm for a duration of 30 min. Flat, round, 8 mm tablets were manufactured using a 10 punches Piccola rotary tablet press (Riva, Buenos Aires, Argentina) rotating at 20 rpm. The tablet hardness was controlled to 120 ± 10 N, tablet weight variation to 270 ± 10 mg, and the room air humidity to 50 ± 5% and temperature to 19 ± 2 °C.

Tablet porosity was determined using Eq. (1). Tablet envelope density was determined dividing the mass by the volume of each tablet. The blend true density values were previously determined (Queiroz et al., 2019).

Table 1
Particulate and bulk powder properties of spray dried MCC, air stream dried MCC and Ibuprofen. Average values are shown ± standard deviation (Queiroz et al., 2019).

Property	Spray dried MCC	Air stream dried MCC	Ibuprofen
D10 (μm) (n = 5)	30.0 ± 0.25	31.1 ± 0.30	16.5 ± 0.08
D50 (μm) (n = 5)	111.6 ± 0.73	118.0 ± 1.60	54.9 ± 0.21
D90 (μm) (n = 5)	236.8 ± 1.55	240.0 ± 2.17	129.0 ± 1.09
Surface area (m^2/g) (n = 3)	1.32 ± 0.01	1.37 ± 0.01	0.22 ± 0.02
True density (g/cm^3) (n = 10)	1.58 ± 0.00	1.57 ± 0.00	1.12 ± 0.00
Bulk density (g/cm^3) (n = 3)	0.33 ± 0.00	0.31 ± 0.00	0.36 ± 0.01
Relative density	0.21	0.20	0.32
Tapped density (g/cm^3) (n = 3)	0.43 ± 0.01	0.40 ± 0.00	0.57 ± 0.01
Hausner Ratio	1.32 (easy flowing)	1.32 (easy flowing)	1.58 (cohesive)
Flow function coefficient (n = 3)	7.0 ± 0.91 (easy flowing)	6.9 ± 0.00 (easy flowing)	3.9 ± 0.11 (cohesive)

$$Porosity = 100 \times \left[1 - \left(\frac{tabletenvelopedensity}{blendtruedensity}\right)\right] \quad (1)$$

3.2. Raman imaging analysis of tablet surface

Drug and excipient distributions on external surfaces and surfaces of internal sections of tablets were investigated by Raman imaging analysis using a RA802 Pharmaceutical analyser (Renishaw, New Mills, UK). First, reference spectra of air stream dried MCC, spray dried MCC, and ibuprofen were acquired. Then, tablets of the blends of ibuprofen and MCC were screened using the StreamLineTM fast imaging method that acquired around 76,000 spectra over the entire surface of each tablet, with a pixel size of 10um/20um, and those spectra were averaged to a single resulting spectrum. The total time of measurement for each individual tablet was 15 min. Images of the drug distribution on the surface of the tablet were generated by non-negative least squares (NNLS) component analysis. Domains of each substance were determined based on the reference spectra acquired for the pure substances. Domains of each substance in the generated images were analysed using Particle Analysis in Renishaw's WiRE software. This software resolves the image domains and determines particle metrics. The numbers of domains of ibuprofen on the entire surface of each tablet and their average equivalent circle diameters were determined.

Principal component analysis (PCA) was performed using the average spectra obtained from Raman imaging analysis. Unscrambler X (Camo Analytics, Oslo, Norway) was used to perform the PCA with full cross validation, using the algorithm Singular Value Decomposition (SVN).

3.3. Disintegration analysis

In vitro disintegration time was determined in water at 37 °C ± 2 °C, using a tablet disintegration tester ZT42 (Erweka, Edison, USA) which complies with Ph. Eur. 2.9.1 (Disintegration of tablets and capsules) (Council of Europe, 2019). Each tablet was placed inside of one basket which were continuously and automatically agitated vertically in the disintegration medium. The disintegration process was observed until the tablets disintegrated into small enough particles that could escape the basket so that no substantial material remained in the basket. Analysis was performed in triplicate.

3.4. FBRM and PVM analysis

FBRM (FBRM G600) and PVM (PVM V19) (Mettler Toledo, Leicester, England) were used to monitor tablet disintegration using a Mettler Toledo Easymax^{TM} 102 system. The disintegration medium was phosphate buffer (pH 7.2). The system used consisted of 100 mL glass vessels with automated internal temperature and agitation control. System specific PTFE (polytetrafluoroethylene) lids allowed for integration of the FBRM and PVM probes. A visual check of the system was possible through an inspection window at the front of the system.

The working volume of the system was 50 mL. Experiments were performed at 37 °C and the agitation rate was 250 rpm using an upward pumping, pitch blade impeller for a minimum of 10 min after the tablet was added to the vessel. The powder or tablet was added to the glass vessel under agitation. PVM and FBRM monitoring was performed throughout the duration of the experiment; FBRM data was recorded every 2 s and two PVM images were recorded every second.

3.5. Dissolution studies

The dissolution studies were carried out using a DT 600 dissolution tester of Ph. Eur. 2.9.3 (paddle) (Erweka, Edison, USA). A volume of 500 mL of phosphate buffer pH 7.2 equilibrated at 37 °C was used as the dissolution medium and the paddle rotation was kept at 50 rpm. Solubility of ibuprofen in the given conditions is 3.74 mg/ml (Dabbagh and Taghipour, 2007). The experiment was conducted using sink conditions; the theoretical concentration of Ibuprofen in the dissolution medium following complete dissolution of 30% w/w ibuprofen tablets was 0.16 mg/ml. Following addition of the tablet sample to the dissolution medium, samples of 0.5 mL volume were withdrawn at 1, 5, 15, 30, 60 and 120, 180, and 240 min intervals in order to determine the dissolution profiles. An additional sample was taken at the 24 h time point to determine the total amount of drug in each tablet tested. At the 24 h time point the tablet had completely disintegrated and complete IBU dissolution was assumed.

All samples were filtered using a 0.45 μm filter and 0.5 mL of fresh, pre-warmed medium was immediately added to the system in order to correct the volume to the sample volume withdrawn. Samples were analysed by HPLC. The % cumulative amount IBU released was calculated and plotted against time.

HPLC analysis was performed using an Agilent 1200 series HPLC system with an UV/Vis detector (Agilent Technologies, Santa Clara, USA). A reversed-phase column (Gemini C-18, 250 × 4 mm × 5 μm, Phenomenex Ltd. UK), mobile phase of acetronitrile and water (60:40, pH adjusted to 2.5) at a flow rate of 1.5 mL/min and injection volume of 20 μL were employed. The wavelength for Ibuprofen detection was set at 215 nm and retention time was 7 min.

4. Results

4.1. Tablet characterisation

The average content of ibuprofen was determined for all tablets analysed and compared to the theoretical content (Table 2). Greatest variance between actual and theoretical content was measured for the 30% w/w ibuprofen loading. Drug content uniformity was also determined with the percentage relative standard deviation less than 7% for all drug loading. Tablet porosity was also determined (Table 2) as it can influence tablet disintegration and dissolution (Ibrahim, 1985; Yassin et al., 2015). Porosity of tablets decreased as ibuprofen content

Table 2
Tablet ibuprofen theoretical and average actual content ± % relative standard deviation (n = 5), blend true density and tablet porosity. * Values obtained from Queiroz et al. (2019).

Theoretical drug concentration (% w/w)	Theoretical drug content (mg)	Air stream dried MCC			Spray dried MCC		
		Actual drug content (mg)	Porosity (%)	True density* (g/cm^3)	Actual drug content (mg)	Porosity (%)	True density* (g/cm^3)
2.5%	6.75	6.63 ± 2.60%	30.3	1.53	6.82 ± 1.57%	32.3	1.52
5%	13.50	13.40 ± 2.21%	30.9	1.52	13.17 ± 2.79%	31.1	1.51
10%	27.00	27.33 ± 2.81%	28.5	1.48	27.06 ± 1.38%	29.7	1.49
15%	40.50	41.68 ± 1.78%	28.6	1.47	41.94 ± 5.02%	28.5	1.47
20%	54.00	54.13 ± 4.26%	26.1	1.45	55.04 ± 2.01%	28.4	1.45
30%	81.00	78.33 ± 6.77%	23.1	1.40	85.34 ± 2.00%	24.10	1.38

increased. The porosity of tablets containing spray dried MCC was slightly greater than tablets containing the air stream dried MCC at all drug loadings except for 15%.

4.2. Raman imaging analysis of tablet surface

Raman spectroscopy did not show differences between the characteristic bands of the MCC tablets (air stream dried and spray dried MCC only), indicating similar chemical identity of microcrystalline cellulose between grades. In respect to the ibuprofen loading, spectral peaks related to ibuprofen increased in intensity when ibuprofen loading was increased (Fig. 1).

Raman images for tablets of all drug loadings were previously published (Queiroz et al., 2019). In this study the number of ibuprofen domains on surfaces of each tablet was determined from these Raman images, as described in section 3.2. The number of ibuprofen domains decreases for the tablets with drug loading above 15% w/w (Table 3), despite an increase in the overall intensity peaks related to ibuprofen (Fig. 1). Above the percolation threshold the domains of ibuprofen start to connect to the neighbouring ibuprofen domains. Thus, one single domain with larger area is counted, instead of numerous smaller neighbouring domains. In the case of the compacted tablets, it results in a change in the drug distribution from dispersion of drug particles in a matrix of MCC (large number of small drug domains) to distribution of MCC in a matrix of drug (smaller number of larger drug domains). The resulting larger domains where characterized by continuously increased equivalent circular diameter of ibuprofen domains with a more pronounced increase between the concentrations of 15% and 20% w/w ibuprofen (Table 3). These results build on the results in the earlier study which qualitatively confirmed the percolation threshold values determined by visual appearance, which can be subjective. In this study the quantitative data obtained related to the number and size of ibuprofen domains provides a less subjective confirmation of the percolation threshold value.

PCA analysis of Raman spectra of the surface of tablets showed that the first principal component (PC-1) captured the effect of drug loading, while the second principal component (PC-2) captured variability within the samples due to both MCC grade and due to ibuprofen drug loading. The scores plot showed samples that are similar or different from each other, i.e. samples geometrically located at distance are dissimilar to each other while neighbouring samples are similar (Fig. 2a). PC-1 and PC-2 explained 88% and 7% of the variance captured by the model, respectively. Raman shifts of 93, 142.8, 639, 748, 835, 1184, 1209, and 1610 cm^{-1} were the variables that mostly contributed to discriminate the samples along the first component of the model (PC-1) (Fig. 2b). Those bands are characteristic of ibuprofen (Sütő et al., 2016) and they were not observed in the spectra of the tablets containing pure MCC (Fig. 1). As stated previously, these peak heights increased with the increase in drug loading. The PCA model showed that tablets containing air stream dried MCC differed from tablets containing spray dried MCC along PC-2. Loadings of PC-2 contained peaks assigned to both, ibuprofen and MCC. PC-2 also showed a general upwards shifting of the baseline with reduction in Raman shift. Both chemical and physical attributes of the tablets may explain this variability in Raman spectra. Differences in tablet porosity was observed with increase in drug loading and between MCC grades (Table 2). Raman spectra can show stronger intensities for more compacted (less porous) samples due to an increased number of scattering molecules that will produce a Raman signal (Gómez et al., 2019). The upwards shift may also be due to Raman fluorescence, which is a material-dependant phenomenon; fluorescence is phenomena intrinsic to MCC. Microcrystalline cellulose is known to be fluorescent mainly due to the presence of lignin (Castellan et al., 2007). Variance related to ibuprofen peaks (e.g. at the shifts 835 and 1610 cm^{-1}) and the main characteristic Raman bands assigned to cellulose (e.g. at 1096 cm^{-1} and within the region 275–550 cm^{-1}) (Wiley and Atalla, 1987) are also present in the loadings of PC-2. The region of 275–550 cm^{-1} is known to hold crystallinity information of cellulosic materials (Agarwal et al., 2010). Thus, the separation of the samples along PC-2 may be an indication that the differences between the spray dried and the air stream dried MCC grades included crystallinity, lignin content, and compact density.

4.3. Disintegration and dissolution

Tablet disintegration using Ph. Eur. 2.9.1 disintegration apparatus showed that all tablets had completely disintegrated in less than 5 min. Differences between tablets containing different drug loadings or MCC grades could not be accurately determined by the Ph. Eur. 2.9.1 apparatus. The tablets investigated contain a high percentage in mass of MCC, which is highly hygroscopic and a noted disintegrant (Rowe et al., 2009). Thus, disintegration happened fast independently of the MCC grade.

The results of the Ph. Eur. 2.9.3 dissolution study showed that increased ibuprofen concentration had a negative impact on the dissolution behaviour of Ibuprofen/MCC tablets (Fig. 3). The effect of ibuprofen loading on drug dissolution was evident for ibuprofen concentrations above the percolation threshold, 20 and 30 %w/w of ibuprofen; time to achieve 100% ibuprofen release increased significantly (Fig. 4). Tablets containing the air stream dried MCC required statistically significantly longer durations to achieve 100% ibuprofen release for all drug loadings, in comparison to tablets containing the spray dried MCC. Tablets containing 30% w/w IBU and air stream dried MCC did not reach 100% release in 240 min. Complete release was confirmed after 24 h. It is also interesting to note that an increase in time to reach 100% cumulative ibuprofen release was observed between 2.5 and 5% drug loading (air stream dried MCC) and 2.5 and 7.5% drug loading (spray dried MCC) respectively (Fig. 4). This change in dissolution behaviour was not related to a percolation threshold of ibuprofen in the MCC matrix but may have resulted due to other factors such as differences in porosity and particulate bonding disintegration behaviour (Desai et al., 2016) and hence dissolution.

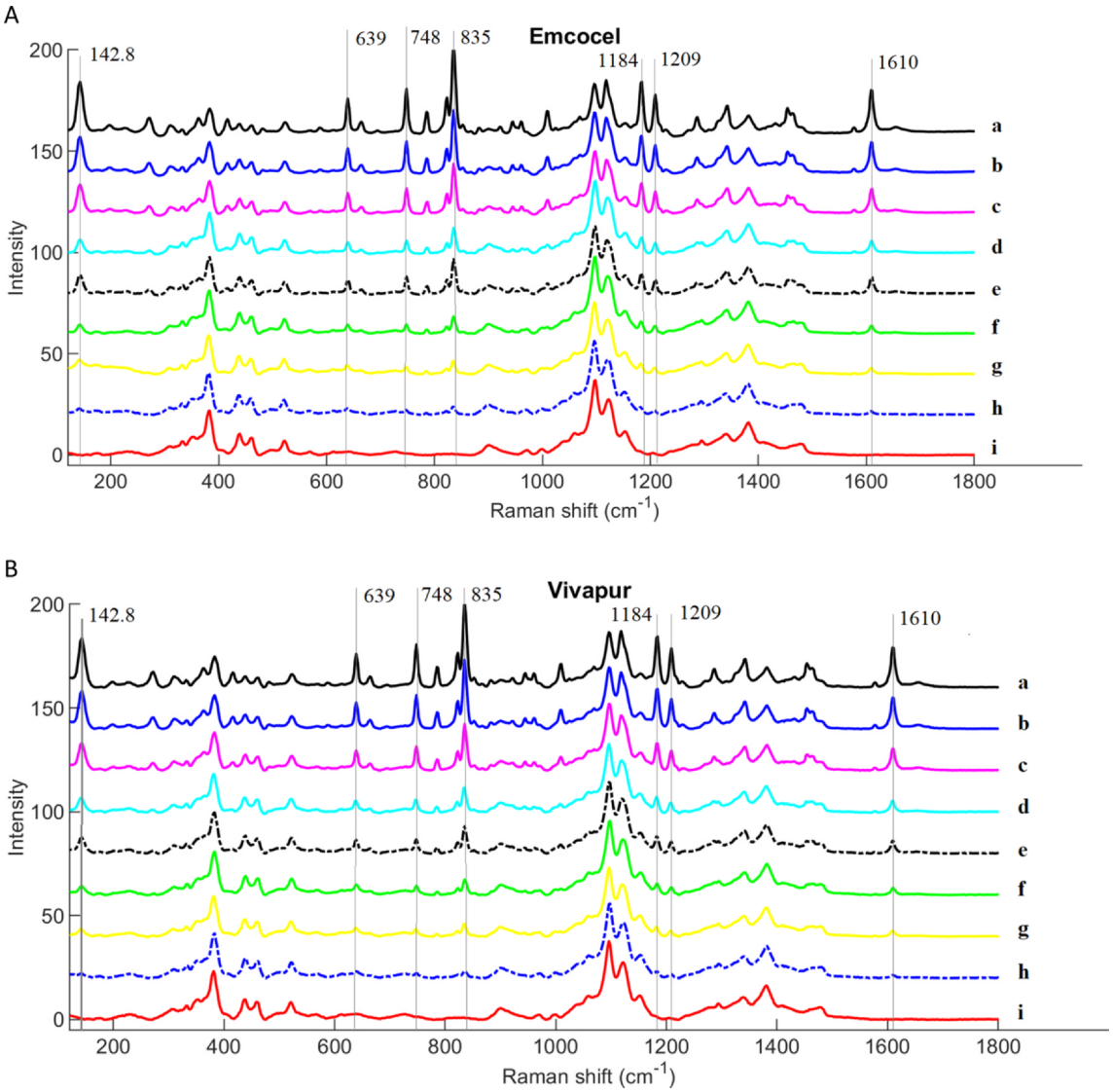

Fig. 1. Average Raman spectra of the surface of (A) Spray dried MCC (Emcocel®) and (B) Air stream dried MCC (Vivapur®) tablets containing a range of ibuprofen loadings: (a) 30%, (b) 20%, (c) 15%, (d) 12.5%, (e) 10%, (f) 7.5%, (g) 5%, (h) 2.5%, and (i) 0% ibuprofen w/w. Vertical lines indicate characteristic peaks of ibuprofen.

Table 3
Number of ibuprofen domains (N) and the equivalent circular diameter (ECD) of ibuprofen domains on the surface of air stream dried MCC and spray dried MCC tablets containing a range of ibuprofen loadings (2.5 to 30% w/w ibuprofen). The number of domains and the equivalent circular diameter values were determined from images generated using Raman image analysis.

% w/w Ibuprofen	Air stream dried MCC		Spray dried MCC tablets	
	N	ECD of ibuprofen domains (μm)	N	ECD of ibuprofen domains (μm)
2.5%	158	69.2	130	62.0
5%	264	70.4	218	59.6
7.5%	264	76.7	343	74.4
10%	462	79.5	475	71.8
12.5%	377	74.3	469	77.1
15%	513	90.5	483	88.6
20%	377	103.5	376	103.4
30%	112	153.7	72	138.9

4.4. FBRM monitoring

FBRM was used as a PAT tool to determine if tablet disintegration played a role in the differences observed between dissolution of tablets containing air stream dried and spray dried MCC grades with increasing drug loading. Two aspects were investigated: the differences among tablets below and above the percolation threshold and the differences between both MCC grades. This analysis was complementary to the pharmacopoeial disintegration test which was not able to capture differences regarding these two aspects. As mentioned previously, FBRM gives particle count, dimension information in real-time (Barrett and Glennon, 1999). It was hoped that the ibuprofen clusters observed in the tablets by Raman imaging could be observed in the disintegration medium and potentially explain the differences in dissolution observed between tablets containing spray dried and air stream dried MCC grades at different drug loadings.

Initially, disintegration monitored by FBRM was performed using spray dried and air stream dried MCC tablets without ibuprofen to determine differences in disintegration due to MCC grade. Both tablets displayed very similar behaviour with a sharp increase in particle counts upon addition of the tablet to the phosphate buffer pH 7.2. Fig. 5

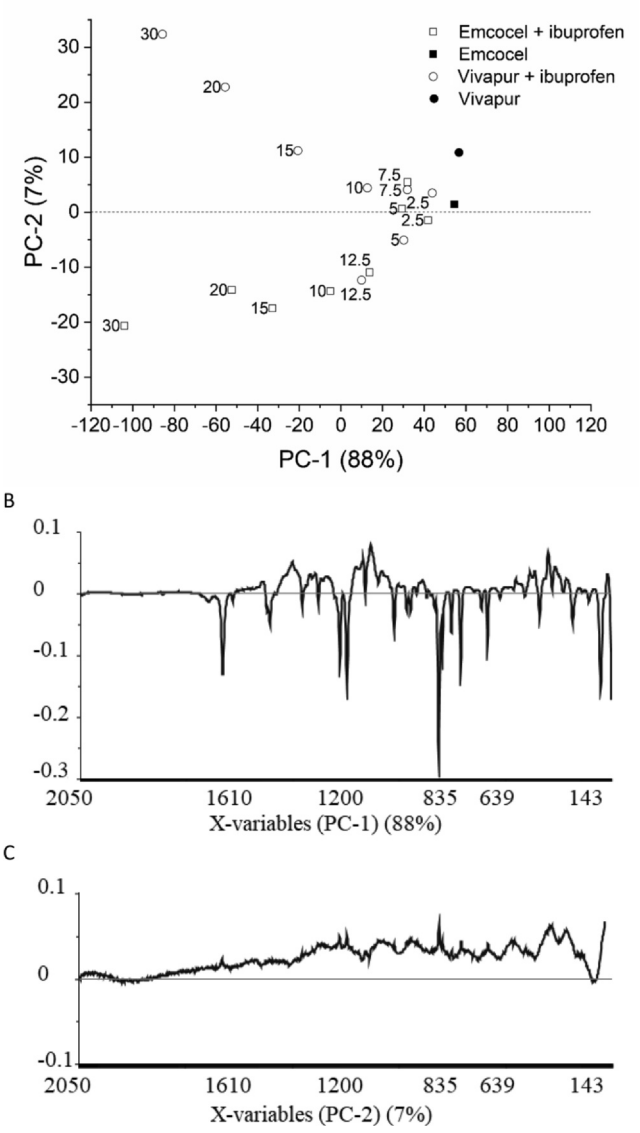

Fig. 2. (A) Scores plot and (B and C) loading plots of the principal component analysis of Raman spectra acquired from spray dried MCC (Emcocel®) and air stream dried MCC (Vivapur®) tablets and tablets containing a range of ibuprofen loadings (2.5% to 30% w/w ibuprofen). PC-1 and PC-2 are the first and the second principal components, respectively.

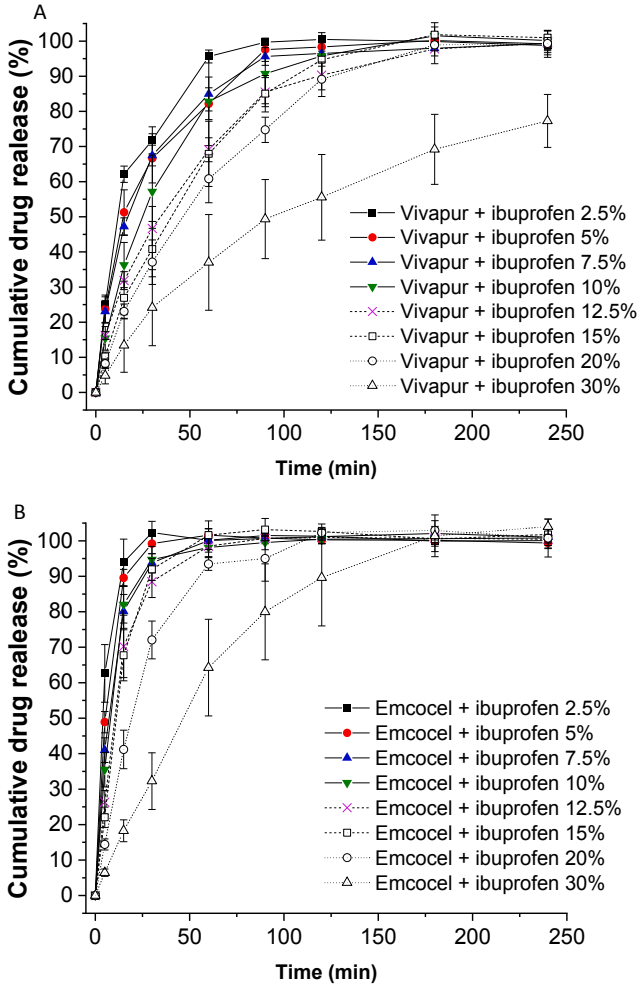

Fig. 3. Dissolution profiles of tablets containing (A) Air stream dried MCC (Vivapur®) and (B) Spray dried MCC (Emcocel®) and different ibuprofen loadings (2.5 to 30% w/w). Dissolution was performed in phosphate buffer pH 7.2 at 37 °C. Average values shown with y-error bars indicating standard deviation, n = 5.

shows that the counts vs time profile for the two MCC grades were very similar, indicating that the tablets disintegrated at the same rate.

Fig. 6 shows the FBRM total counts vs time for ibuprofen tablets added to the disintegration medium for the first 30 min. All tablets show a rapid increase in counts for the first 5 min approximately, indicating that, as with the tablets of air stream dried and spray dried MCC without ibuprofen, tablet disintegration began immediately upon addition of the tablet to the medium for all ibuprofen loadings. A similar profile is seen for each tablet of spray dried MCC regardless of ibuprofen loading. The counts increased sharply in the first 30 s after addition to the medium and then continued to increase at a slower rate for the following minutes. Overall, air stream dried MCC tablets showed a less consistent total counts versus time profile for different drug loadings in comparison to spray dried MCC tablets. When the different ibuprofen loadings were compared, the loadings of 20% and 30% w/w ibuprofen showed reduced profiles compared to lower drug loadings. The total counts profiles for tablets containing air stream dried MCC was also lower in comparison to tablets containing spray dried MCC, for all ibuprofen loadings (Fig. 7). These differences were more pronounced above the percolation threshold > 15% ibuprofen.

Due to the variability in the total number of counts for each tablet, a relative increase in FBRM counts was measured for each tablet to enable comparison during the disintegration process. Fig. 8 shows the time required to reach 50, 60, 70, 80, 90% total counts. All tablets were tracked for 30 min as the disintegration process for all tablets was considered complete at this time point. Thus, 100% total counts was considered the total counts at 30 min. The overall trend showed a longer time for tablets containing air stream dried MCC compared to spray dried MCC, indicating a slower disintegration rate.

An indication of particle size distribution during disintegration was obtained from the FBRM chord length distributions (CLD) and square weighted chord length distributions (SQW CLD). These distributions were automatically generated by the iC FBRM software. The chord length of each particle was measured individually and counts (n_i) of similar sizes stored in a channel (or bin) of a defined size range to generate CLD. SQW CLD are useful for visual comparison of systems by emphasising differences in the coarse counts (100 – 1000 μm). SQW CLD were achieved by normalising the counts per channel, converting unweighted counts (n_i) to weighted counts (y_i) via:

$$y_i = w_i . n_i \quad (2)$$

The weights w_i are obtained from the channel midpoints M_i via:

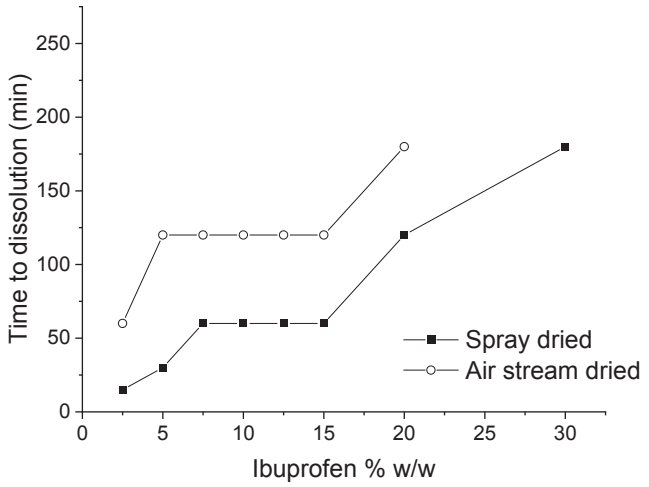

Fig. 4. Time to reach 100% ibuprofen release during dissolution of tablets containing spray dried and air stream dried MCC and different ibuprofen loadings (2.5 to 30% w/w). Tablets containing air stream dried MCC and 30% w/w of ibuprofen did not reach 100% release in 240 min. However, complete release was confirmed after 24 h. Dissolution was performed in phosphate buffer pH 7.2 at 37 °C. Average values shown with y-error bars indicating standard deviation, n = 5.

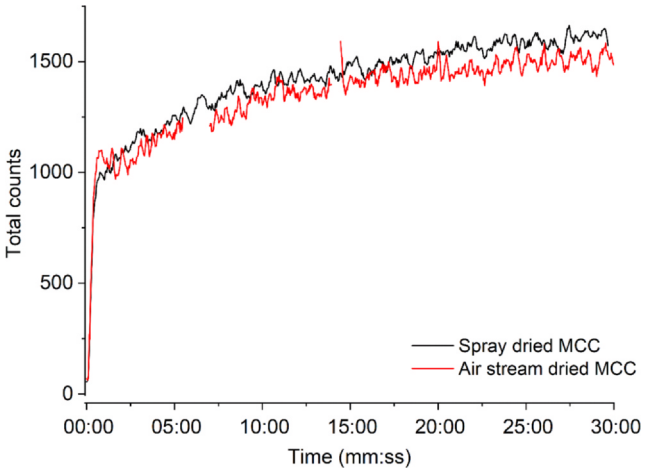

Fig. 5. Focused Beam Reflectance Measurement (FBRM) counts 1–1000 μm versus time for tablets containing air stream dried and spray dried MCC in phosphate buffer pH 7.2, and temperature of 37 °C.

$$w_i = \frac{M_i^{\gamma}}{\sum_{j=1}^{N} M_j^{\gamma}} \bullet N \quad (3)$$

where γ is 2 for the square weight, N is the number of channels, which was 90 in this study, i = 1, 2, …, N and j = 1, 2, …, N.

Representative tablets with 12.5, 15% w/w, and 30% w/w ibuprofen loadings, after 5 min of dissolution, are shown in Fig. 9. CLD for all drug loadings investigated are available in the supplementary material. Coarse counts account for a much larger proportion of the mass of material compared with fine counts (1–10 μm). While the CLDs for both systems have a similar shape profile the increased number of total counts and shorter chord length counts was evident for the spray dried compared to the air stream dried MCC. Fine counts may be related to disaggregation of MCC particles during disintegration. MCC is composed of cellulose fibrils agglomerated into larger particles (Queiroz et al., 2019). Therefore, particle disaggregation during disintegration can result in smaller particle sizes observed in the buffer compared to the particle size distribution reported for dry MCC particles (Table 1). When the square weighted CLDs are compared there is a distinct shift to the right for air stream dried, highlighting the increased particle size present 5 min after the tablet addition to the buffer. An increase in fine counts (1–10 μm) present in the spray dried MCC system suggested that tablets of the spray dried MCC disintegrated more effectively than tablets of the air stream dried MCC at a 30% w/w ibuprofen loading. For loading below the percolation threshold, a similar trend was seen although the shift to the right for air stream dried in the square weighted CLD is less pronounced. This is exemplified by 12.5% w/w ibuprofen tablets in Fig. 9.

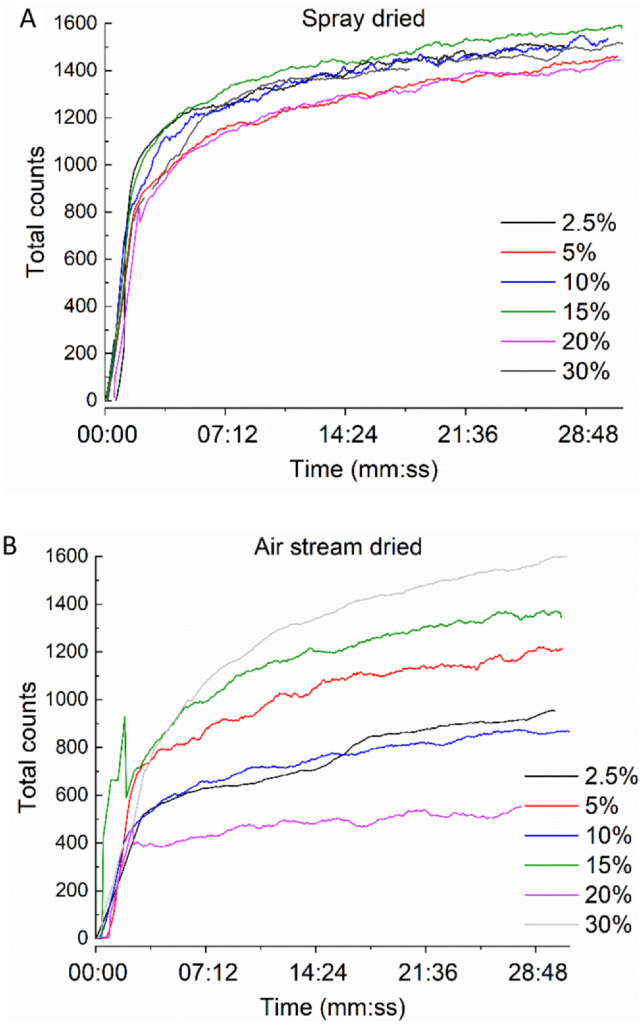

Fig. 6. Focused Beam Reflectance Measurement (FBRM) total particle counts (counts 1–1000 μm) versus time for tablet containing (A) Spray dried MCC and (C) Air stream dried MCC and different ibuprofen loadings (2.5 to 30% w/w) in phosphate buffer pH 7.2 and temperature of 37 °C.

The plots of chord length distributions at different time points during disintegration for all tablets were generated (supplementary data) and selected profiles shown in Fig. 10. The increase in counts over time happens similarly across all chord lengths for a same tablet, i.e. the distribution did not show a shape change at different time points. Interestingly, the increase in count is clearly more significant up to 5 min. After 5 min, the change chord length distributions were comparatively small.

Based on the results shown in Fig. 10, the greatest degree of disintegration occurred in the first 5 min, the cumulative drug release at 5 min was plotted against drug loading to investigate the differences in drug release below and above the threshold during tablet disintegration (Fig. 11). Similar graphical approaches have been previously used to determine the percolation threshold from disintegration and dissolution (Kimura et al., 2007; Wenzel et al., 2017). Cumulative ibuprofen release

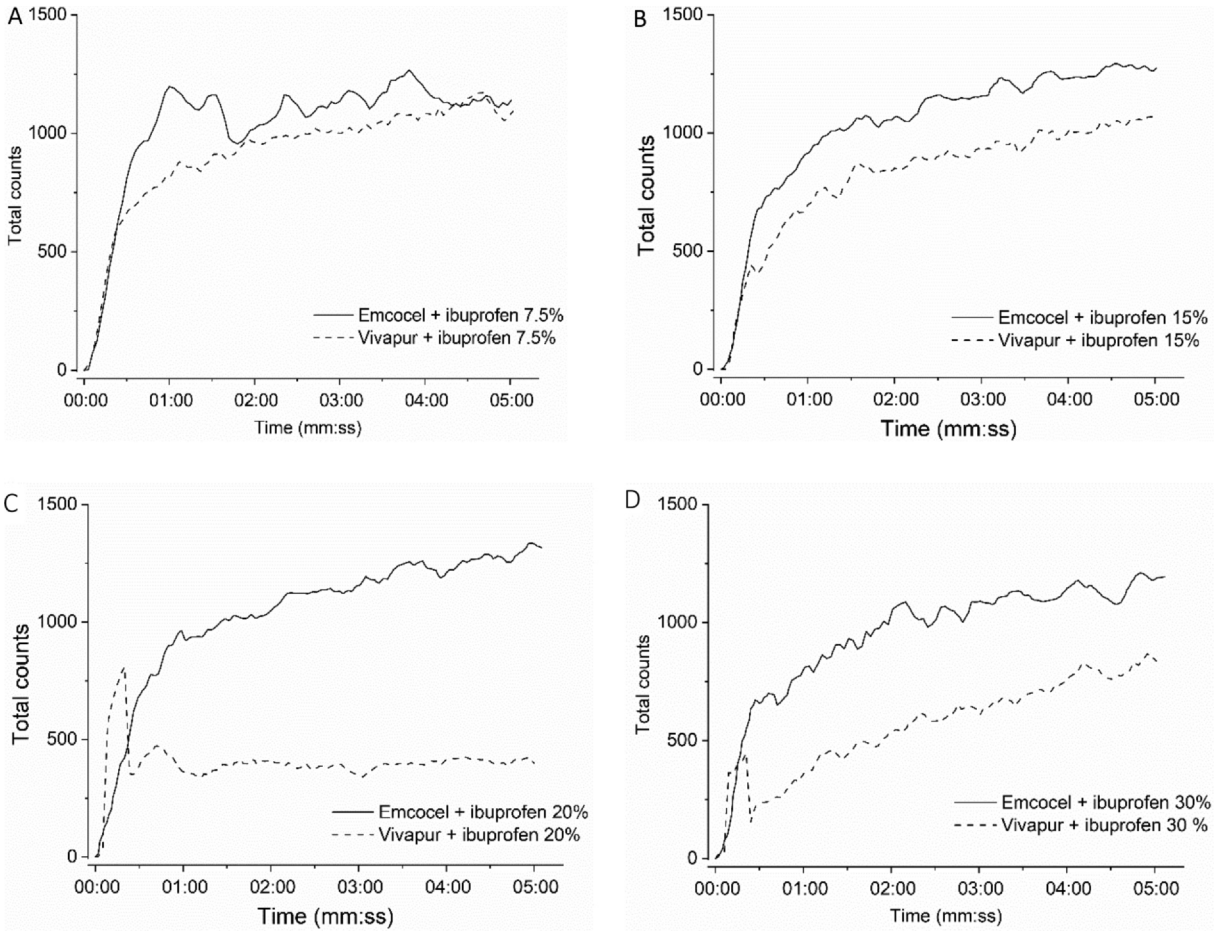

Fig. 7. Focused Beam Reflectance Measurement (FBRM) total counts over time for air stream dried MCC (Vivapur®) and spray dried MCC (Emcocel®) tablets containing ibuprofen (A) 7.5%, (B) 15%, (C) 20%, and (D) 30% w/w in phosphate buffer pH 7.2 and temperature of 37 °C.

decreased sharply from 2.5 to 15% w/w of ibuprofen loading. However, at drug loadings above the reported percolation threshold (20% w/w and 30% w/w ibuprofen) the reduction in drug release with increase in drug loading was decreased. Tablets containing the air stream dried MCC showed significantly lower drug release for all drug loadings in comparison to tablets containing the spray dried MCC. These findings confirmed a step change in drug dissolution behaviour at drug concentrations above and below the predicted percolation threshold following tablet disintegration.

4.5. PVM analysis

PVM analysis was performed to provide real-time images of particles in dissolution medium during tablet disintegration. Besides the images, PVM relative backscatter index was used as a quantitative measure of disintegration. Initially, images were collected using the PVM probe for ibuprofen powder and both MCC only tablets in buffer. The ibuprofen particles had a distinct rod-shaped habit (Fig. 12a). Dispersed ibuprofen powder was present as both discrete particles and aggregates. The ibuprofen particles appeared to be between 100 and 300 μm in length and 30 and 50 μm in width. When compared with the particle size for the dry powder from laser diffraction (Table 1), where the D50 was 55 μm, it appears that larger ibuprofen particles in the PVM images may be aggregates.

PVM images of the disintegrated spray dried MCC tablet (Fig. 12b) indicated that fine material was present along with uniform distinct particles having a rough surface. Images of disintegrated air stream dried MCC tablet (Fig. 12c) are similar to spray dried MCC. These images would support the presence of fine particles observed during FBRM analysis, Figs. 9 and 10. These appeared to be rod shaped particles present which are similar in appearance to the ibuprofen particles.

Side by side comparison of PVM images of disintegrated tablets containing spray dried and air stream dried MCC with equivalent ibuprofen loading showed that it is difficult to distinguish definite differences between the two systems. One difference noted was that air stream dried tablets showed more elongated particles (Fig. 13). There are rod shaped particles present in the air stream dried suspension (Fig. 12), hence it was not possible to distinguish whether this rod-shaped material following the 15% w/w ibuprofen tablet disintegration is ibuprofen or MCC.

Relative Backscatter Index (RBI) measured by PVM is the relationship between the incident and the detected light. As disintegration progresses the number of particles in the media increases due to fragmentation of larger particles to smaller particles and RBI increases. The change in the PVM RBI versus time during disintegration does indicate differences for tablets containing 20% and 30% ibuprofen loading tablets compared to tablets containing lower ibuprofen loadings (Fig. 14). For ibuprofen loadings below the percolation threshold the RBI for both spray dried and air stream dried MCC tablets was similar. The air stream dried MCC tablets with a 20 and 30% w/w ibuprofen had a significantly lower final RBI during disintegration compared to air stream dried MCC (Fig. 14d).

5. Discussion

The research presented was conducted to determine whether a percolation threshold value, previously determined for ibuprofen/ MCC

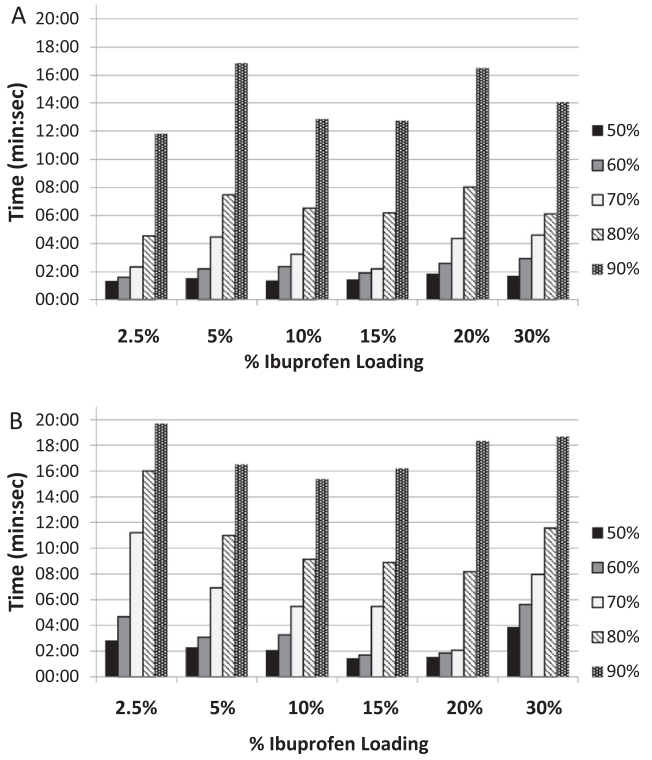

Fig. 8. Time to reach percentage of total counts measured by FBRM for tablets during disintegration containing (A) Spray dried MCC and (B) Air stream dried MCC and different ibuprofen loadings (2.5 to 30% w/w) in phosphate buffer pH 7.2 at 37 °C. Percentages expressed relative to total counts at 30 mins considered 100%.

blends using percolation theory and compression data (Queiroz et al., 2019), could translate to tablet disintegration and dissolution data. Previous studies determined a percolation threshold value experimentally from disintegration and dissolution data (Kimura et al., 2007; Stillhart et al., 2017; Wenzel et al., 2017). For ibuprofen/MCC blends, the existence of a percolation threshold was predicted mathematically and confirmed experimentally from blend properties and a compaction behaviour perspective (Queiroz et al., 2019). In the present study, disintegration and dissolution experiments were carried out to experimentally confirm whether the percolation threshold, previously predicted for ibuprofen/MCC blends, causes a step change in tablet disintegration and dissolution behaviour.

Dissolution testing confirmed the presence of the percolation threshold in the region previously reported. A change in behaviour above the percolation threshold was observed during dissolution; % drug released at 5 min during the tablet disintegration process (Fig. 11), and in relation to the time to achieve complete dissolution (Fig. 4). Blends above the percolation threshold showed slower dissolution profiles. (Kimura et al., 2007) also revealed a decreased disintegration performance above the critical loading of a poorly water-soluble drug. In the case of tablets containing MCC and ibuprofen, it was hypothesised that the connected MCC particles would form the water-conducting clusters promoting disintegration. Above the threshold predicted a continuous cluster of ibuprofen particles is formed. Relative to MCC, ibuprofen is poorly water soluble, and the formation of continuous ibuprofen clusters would decrease disintegration. Thus, the explanation for the reduction in dissolution above the percolation threshold can be attributed to the combined effect of decreased drug surface area to mass due to the presence of continuous clusters evidenced by Raman imaging and a change in the disintegration process.

In this study, Raman imaging and image domain analysis were combined to confirm percolation threshold in pharmaceutical tablets.

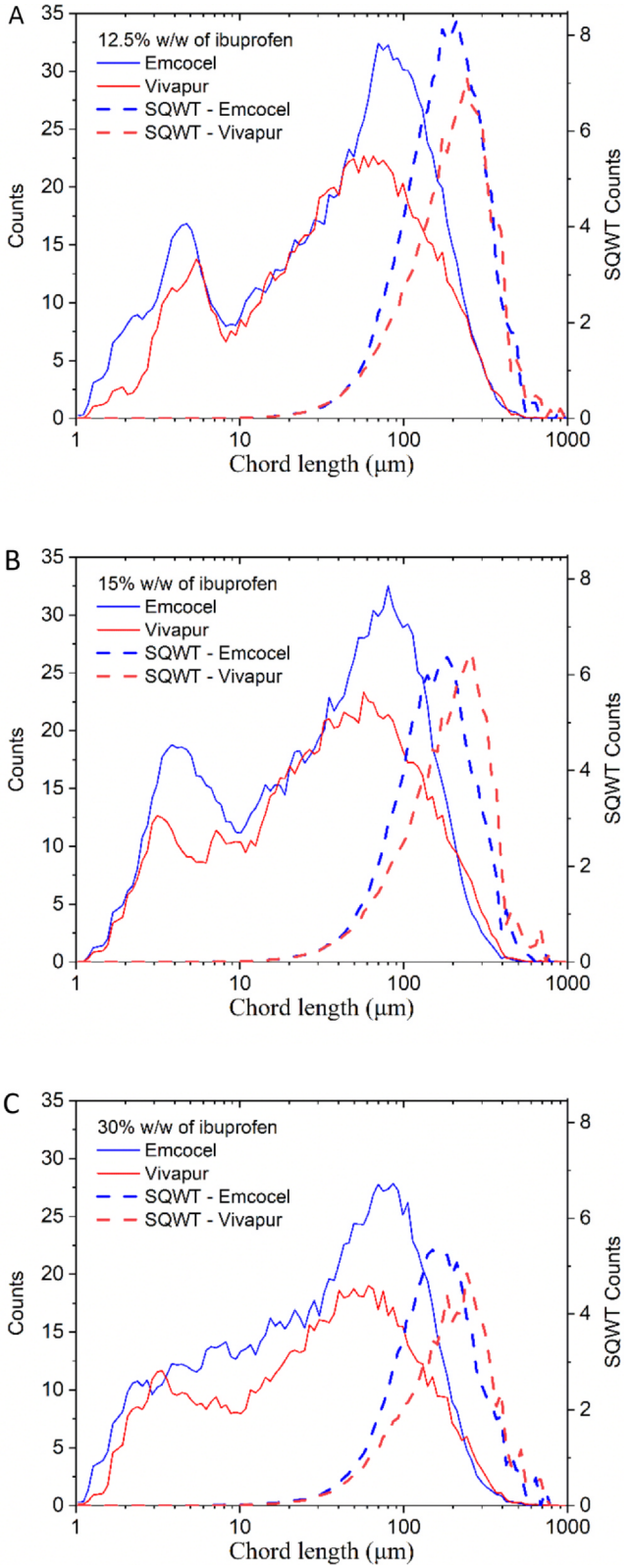

Fig. 9. Focused Beam Reflectance Measurement (FBRM) chord length distributions and square weighted (SQWT) chord length distributions for Emcocel® (spray dried MCC) and Vivapur® (air stream dried MCC) tablets with ibuprofen loading (A) 12.5%, (B) 15%, and (C) 30% w/w, 5 min after addition to the disintegration medium, phosphate buffer pH 7.2 and temperature of 37 °C.

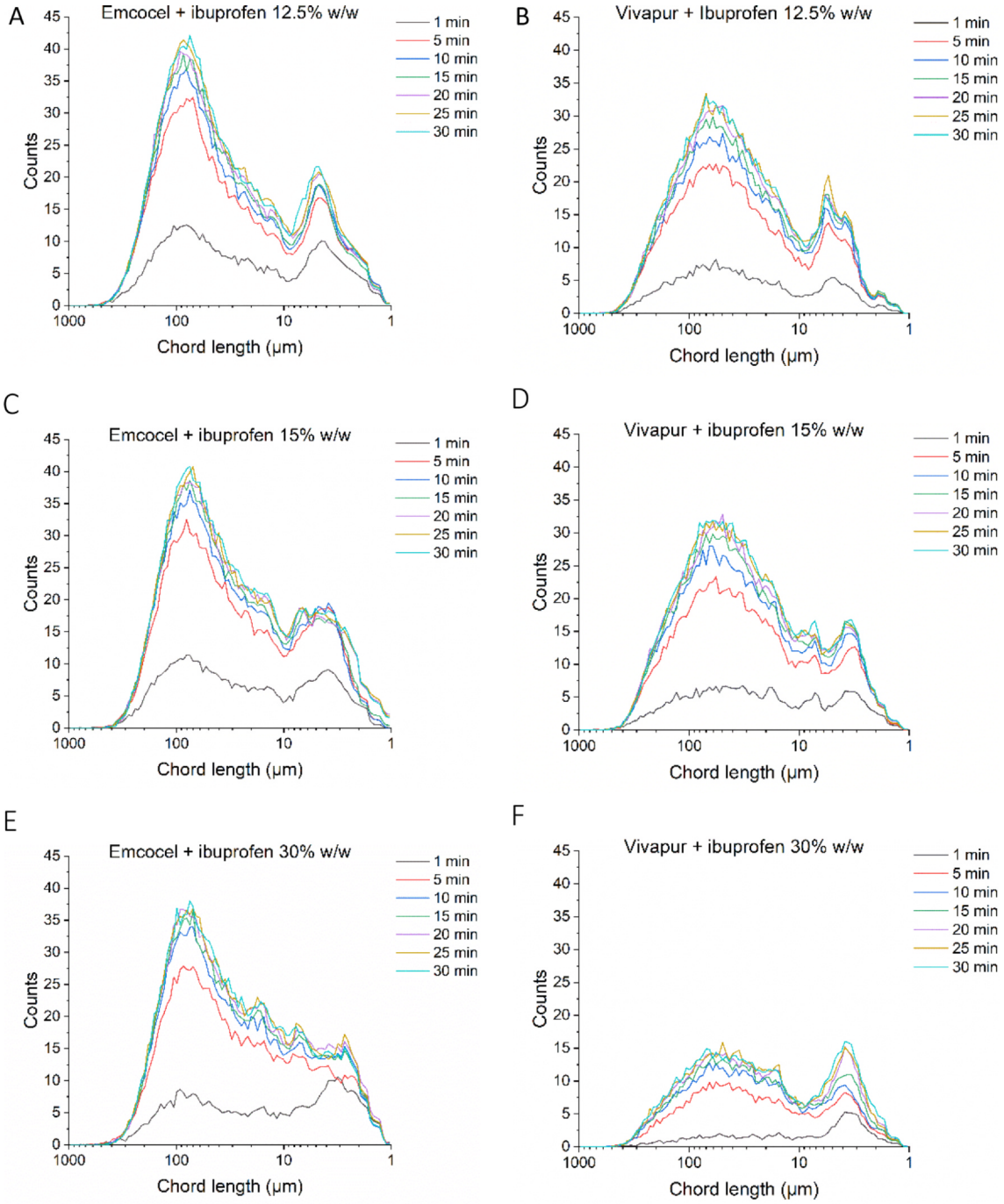

Fig. 10. Focused Beam Reflectance Measurement (FBRM) chord length distributions for tablets with ibuprofen loadings of 12.5%, 15%, and 30% w/w and spray dried MCC (Emcocel®)(A, C, and D) and air stream dried MCC (Vivapur®) (B, D, and F) at different times after addition of tablet to the disintegration medium (phosphate buffer pH 7.2 and temperature of 37 °C).

The methodology developed confirmed the percolation threshold previously predicted for the binary blend investigated (Queiroz et al., 2019) by an increasing number of drug cluster up to the percolation threshold and reduction above due to the formation of continuous clusters. For the drug loading above 15%, the number of ibuprofen domains dramatically decreased, and their equivalent circle diameter increased which confirms the cluster formation and would contribute to a slower rate of ibuprofen dissolution due to a reduced surface area to mass ratio.

The influence of the presence of continuous ibuprofen clusters on tablet disintegration was difficult to establish by pharmacopoeial disintegration testing. However, the use of FBRM and PVM to interrogate the tablet disintegration process with respect to drug loading demonstrated a change in behaviour above the percolation threshold, particularly for tablets containing air stream dried MCC (Figs. 7 and 14). In this study, the dissolution of the disintegrated particles could not be monitored by FBRM nor PVM due to similarity in morphology of the disaggregated MCC particles and ibuprofen particles (Fig. 13) and the insoluble nature of MCC in the disintegration medium. However, it may be possible to monitor drug dissolution for formulations with high drug loadings and soluble excipients, such as lactose, using PVM and FBRM techniques.

The secondary objective of this study was to investigate the influence of MCC grade on disintegration and dissolution behaviour relative

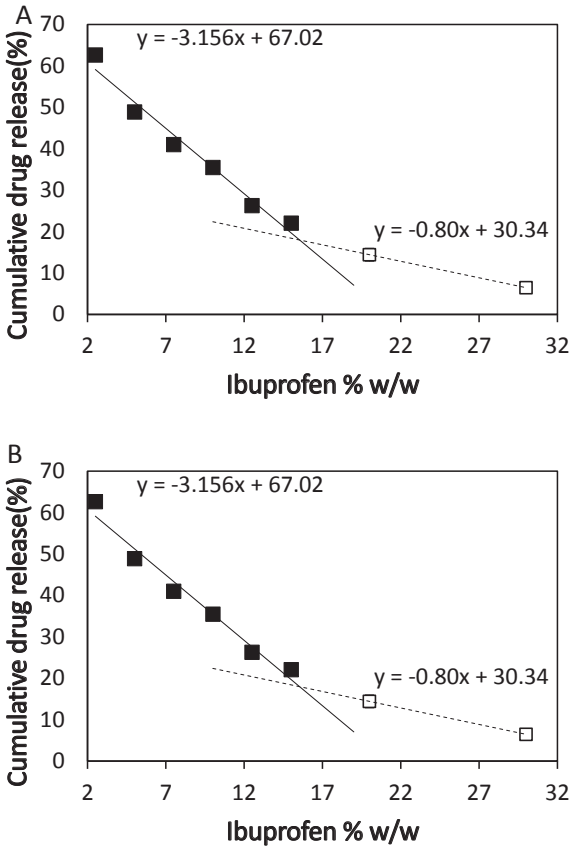

Fig. 11. Estimation of percolation threshold based on the dissolution cumulative release of ibuprofen from the tablets containing (A) Air stream dried MCC and (B) Spray dried MCC, at 5 min of dissolution. The time of 5 min was chosen to represent the differences in behaviour during disintegration.

to the percolation threshold. Despite the MCC grades having similar bulk properties, the interaction of each grade with the model drug ibuprofen resulted in differing dissolution behaviour. In all cases, the tablets containing the air stream dried grade showed slower disintegration and dissolution rates. Air stream dried MCC tablets showed a reduction in disintegration rate above the percolation threshold value while spray dried MCC did not (Figs. 6 and 14). Air stream dried MCC tablets displayed slower dissolution rates (Fig. 4) across all drug loading.

The mechanistic explanation for the differences in disintegration and dissolution behaviour observed between MCC grades investigated is unclear. Raman image analysis showed similar distribution and size of ibuprofen clusters for both tablets containing both MCC grades (Table 3). However, tablet porosity differed between MCC grades, with tablets produced from the air stream dried MCC grade being slightly less porous (Table 2). Tablet porosity is a function drug loading, and for blends of poorly compressible drugs with MCC, porosity is reduced above the percolation threshold value (Queiroz et al., 2019). MCC samples with less dense crystalline regions were reported to swell more as they are more accessible for the water molecules, and the cohesive forces between the chain segments are weaker, in comparison to the crystalline domains (Desai et al., 2016; Schott, 1992). Therefore, differences in MCC crystallinity could also contribute to differences in tablet disintegration behaviour. Further studies are required to determine the exact mechanisms causing in the reduced dissolution rates for tablets containing air stream dried MCC compared to the spray dried grade.

It was challenging to discriminate between the effects of tablet porosity and percolation threshold in relation to tablet disintegration. The compaction parameters and bonding mechanism of particles during compaction directly impact tablet porosity, the ingress of the disintegration medium, MCC swelling and hence tablet disintegration (Yassin et al., 2015). Despite confounding variation observed in tablet porosity in this study, a clear step change in dissolution behaviour was observed for tablets with drug loadings above the percolation threshold.

6. Conclusions

Dissolution data showed that a percolation threshold value previously determined for ibuprofen/MCC binary blends, from compaction data, translated to tablet dissolution data. Slower ibuprofen dissolution behaviour was observed for tablets above the predetermined percolation threshold. This confirmed the presence of the percolation threshold and its relevance to dissolution studies. In addition, slower dissolution was observed for all tablets containing an air stream dried MCC grade,

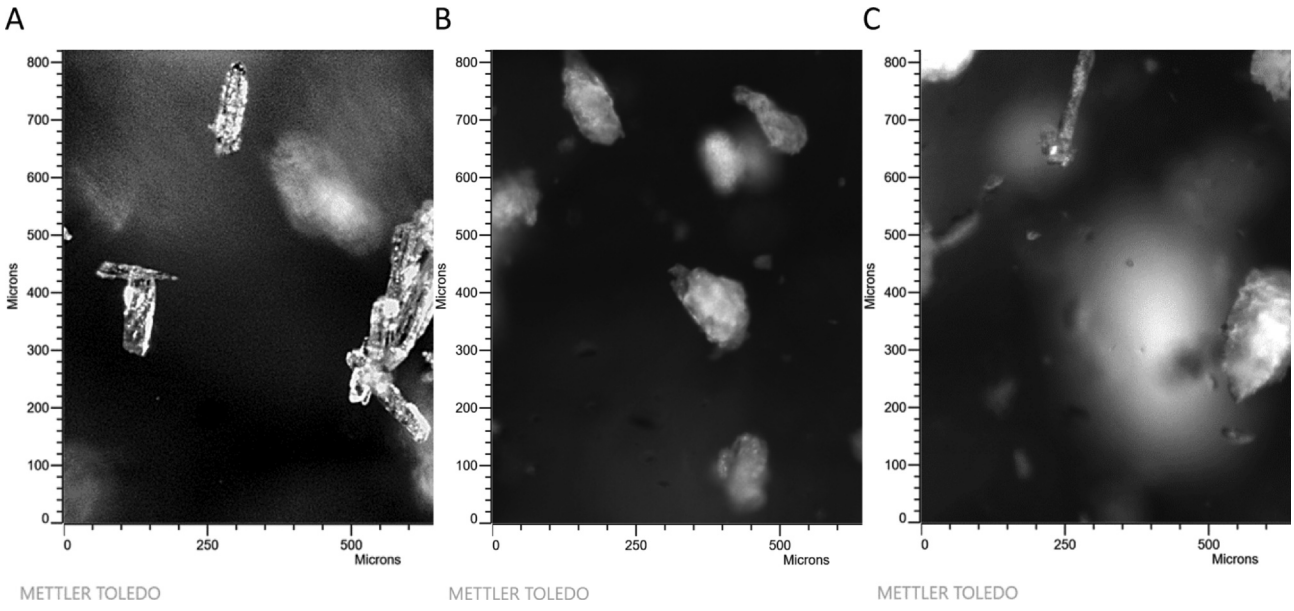

Fig. 12. PVM images of (A) ibuprofen powder, and (B) Spray dried MCC (Emcocel®) and (C) Air stream dried MCC (Vivapur®) particles following tablet disintegration in phosphate buffer pH7.2 and temperature of 37 °C.

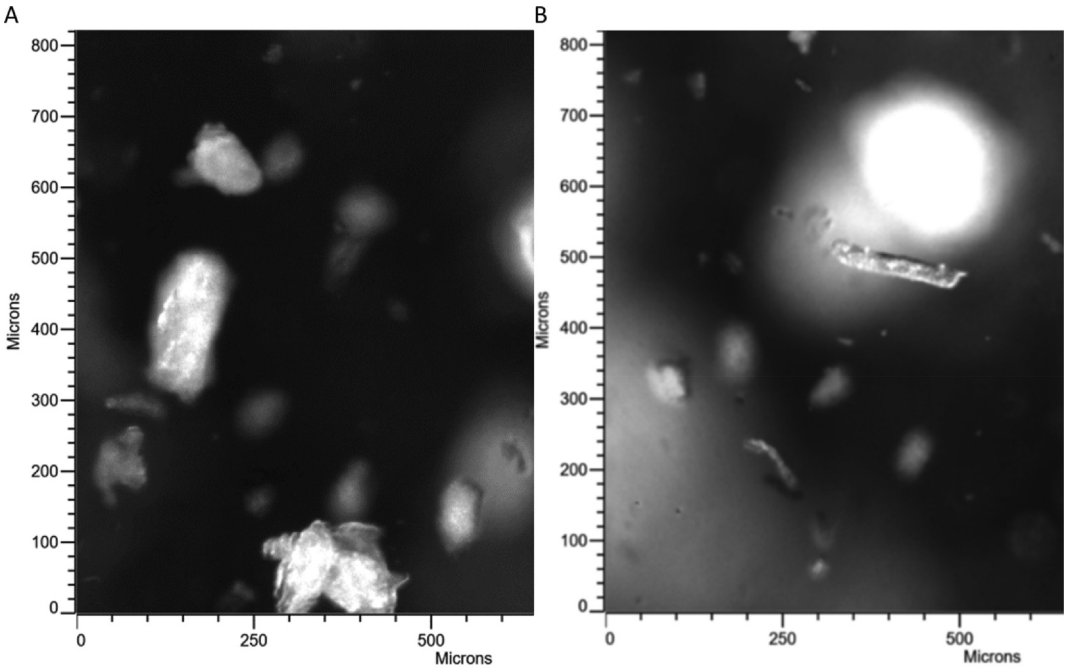

Fig. 13. Representative PVM images of particles following disintegration of (A) Spray dried MCC and (B) Air stream dried MCC tablets with a 15% w/w ibuprofen loading in phosphate buffer pH7.2 and temperature of 37 °C.

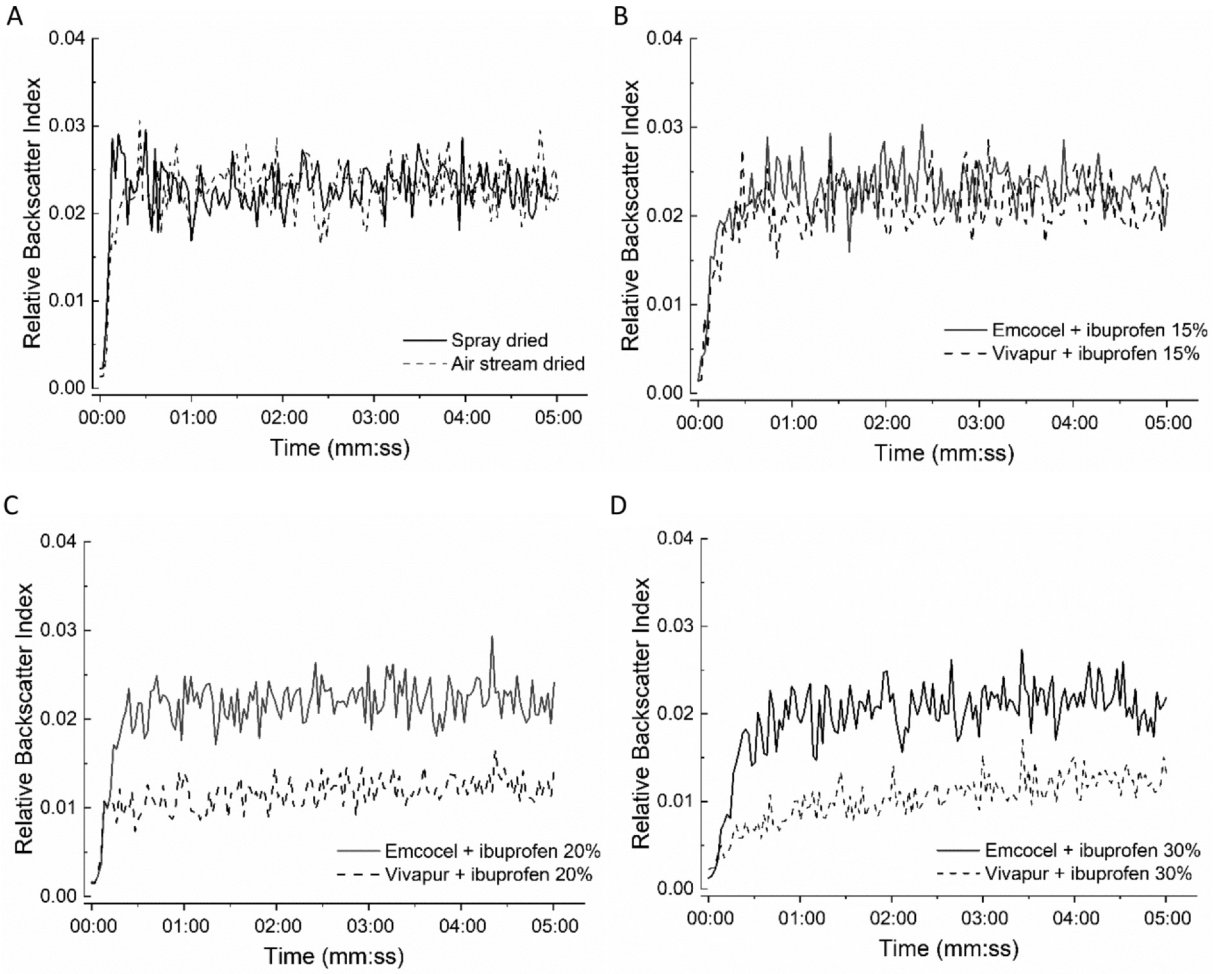

Fig. 14. Relative Backscatter Index (RBI) vs time following disintegration of spray dried MCC (Emcocel®) and air stream dried MCC (Vivapur®) tablets (A) 0% w/w, (B) 15% w/w, (C) 20% w/w and (D) 30% w/w ibuprofen in phosphate buffer pH7.2 and temperature of 37 °C.

compared to a spray dried MCC grade. FBRM and PVM showed less efficient disintegration above the percolation threshold for tablets containing air stream dried MCC. The results experimentally demonstrate that both larger drug domains, quantified by Raman imaging, and a less efficient tablet disintegration measured by FBRM and PVM (in the case of air stream dried MCC) contributed to slower ibuprofen dissolution profiles above the percolation threshold.

CRediT authorship contribution statement

Ana Luiza P. Queiroz: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Barbara Wood:** Methodology, Formal analysis, Investigation, Writing - original draft. **Waleed Faisal:** Methodology, Investigation. **Fatma Farag:** Investigation. **Hazel Garvie-Cook:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - review & editing. **Brian Glennon:** Writing - review & editing. **Sonja Vucen:** Writing - review & editing, Supervision. **Abina M. Crean:** Conceptualization, Methodology, Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Dissolution tests were carried out by Ms. Roisin Keane and Ailbhe Kearney, School of Pharmacy University College Cork.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2020.119838.

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